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Improve the Outcome of Autologous Hematopoietic Cell Transplantation!

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INTRODUCTION

Autologous hematopoietic cell transplantation (AHCT) is a frequently used treatment modality for children and adult patients with hematologic malignancies and selected solid tumors. The conditions for which AHCT has been employed successfully are listed in Table 1. Note that "clinical use" is not synonymous with "established superior therapy."

In the United States, approximately 14,000 patients were treated with AHCT during the year 2000 (M.M. Horowitz, MD, oral communication, 2001). In other parts of the world where AHCT is offered to cancer patients, a similar number of patients received this treatment, according to this author's estimate, so that last year the total number of AHCT recipients ranged from 25,000 to 35,000.

Published data from numerous transplantation centers indicate that long-term disease-free survival (DFS) rates vary from approximately 20% to more than 80% depending on the patient's remission status at the time when preparation for AHCT is begun. Relapse of the underlying disease is the major source of treatment failure. The clinical use of AHCT with all of its potential risks and side effects is justified only when 3 conditions are met: that the overall treatment approach is optimized, that patients receive treatment according to clinical research protocols, and that outcome data are reported in the scientific literature and/or to organized transplantation registries (Autologous Bone Marrow Transplant Registry in the United States [ABMT], European Group for Blood and Marrow Transplantation [EBMT]).

Several opportunities that either singly or in combination can contribute to improved outcome results of AHCT are listed in Table 2. The following discussion is intended to demonstrate that advances made through successful translational research have led to favorable results in the area of AHCT, with treatment of non-Hodgkin's lymphoma (NHL) serving as an example.

TIMING OF AHCT WITH RESPECT TO REMISSION STATUS

The amount of tumor burden is indirectly proportional to long-term DFS. Another factor contributing to treatment failure (relapse) is drug resistance of malignant cells. Therefore, AHCT during first remission of a disease such as follicular lymphoma is likely to be more successful than AHCT during subsequent remissions [1-3]. In a prospective phase II trial performed from 1988 to 1994, we studied 37 eligible adult patients with previously untreated stage III or IV follicular NHL [4]. After the patients achieved a state of minimal residual disease (MRD) with standard-dose chemotherapy, bone marrow was obtained under general anesthesia and treated with a combination of monoclonal antibodies (MoAbs) directed against B-cell epitopes and complement followed

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Table 1. *Clinical Use of Autologous Hematopoietic Cell Transplantation*

Acute leukemia (myelogenous, lymphoblastic)
Chronic lymphocytic leukemia
Non-Hodgkin's lymphoma
Multiple myeloma
Neuroblastoma and other selected pediatric tumors
Solid tumors in adult patients (breast cancer, ovarian cancer, testicular cancer)

Table 2. *Opportunities to Improve the Outcome of Autologous Hematopoietic Cell Transplantation (AHCT)*

Timing of AHCT with respect to remission status
Selection of myeloablative doses and combinations of drugs with or without irradiation
Optimizing the graft, ie, removal of clonogenic tumors without loss of activity for hematopoietic reconstitution
Post-AHCT therapy to consolidate remission (cytokines, monoclonal antibodies, vaccines, cells, involved-field radiation)

Table 3. *Problem Areas of Autologous Hematopoietic Cell Transplantation**

Age limit
Regimen-related toxicity
Graft failure
Opportunistic infections
Relapse
Secondary and second malignancies
Quality of life
Cost/charges

*Problems are listed in chronological order as they occur during the course of an autologous transplantation procedure. The main problem is relapse of the underlying cancer.

by cryopreservation. Patients were exposed to a high-dose preparatory regimen that consisted of fractionated total body irradiation (FTBI), etoposide (VP-16), and cyclophosphamide (CY) with subsequent autografting. After an observation time of 6 to 12 years, the disease-specific survival rate was 97%; 32 (86%) of the 37 enrolled patients were alive; and 23 patients (62%) were in continued complete remission, whereas the actuarial relapse rate was 30% (Figure 1). It appears that the natural history of follicular lymphoma has been successfully altered, resulting in excellent overall survival (OS) and DFS rates. In contrast, 66 patients with either recurrent or transformed follicular lymphoma treated at our center with myeloablative therapies and AHCT (MoAb-purged bone marrow or peripheral blood cell grafts) attained clearly less favorable OS (52%) and DFS (41%) rates [5].

SELECTION OF MYELOABLATIVE DOSAGE AND COMBINATIONS OF DRUGS WITH OR WITHOUT IRRADIATION

The sole purpose of the preparatory regimen administered before AHCT is to eradicate the underlying diseases by destroying—ideally—all malignant cells. Dose escalation studies of drugs and drug combinations have led to regimens that have proven to be potent and effective against lymphoid malignancies, in particular NHL. We have employed a triple combination of FTBI, VP-16, and CY at maximum tolerated doses (MTD) for patients younger than 60 years who had not been previously treated with irradiation [6]. For patients older than 60 years or patients who had received prior radiotherapy, FTBI was replaced by 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) at MTD [6]. Since the inception of our program in 1987, a total of 439 patients with persistent or relapsed NHL have received 1 of these 2 preparatory regimens. Actuarial survival and relapse data are presented in Figure 2A and B.

It is noteworthy that the FTBI-containing regimen was more toxic during the early posttransplantation phase but still led to improved long-term OS rates. In particular, radiation was not associated with an increased incidence of second or secondary malignancies after AHCT. The 2 relapse curves are virtually superimposable, confirming our earlier reported observations [7].

A different and potentially more successful approach was chosen by investigators at the University of Washington [8]. They replaced FTBI with radiolabeled MoAbs directed against CD20 to deliver radiation targeted to tumor sites and attained promising results in a clinical phase I/II trial. Two other studies employing the same treatment principle are underway at the City of Hope National Medical Center (S.J. Forman, MD, written communication, 1999) and at the University of Nebraska (J.M. Vose, MD, written communication, 2001).

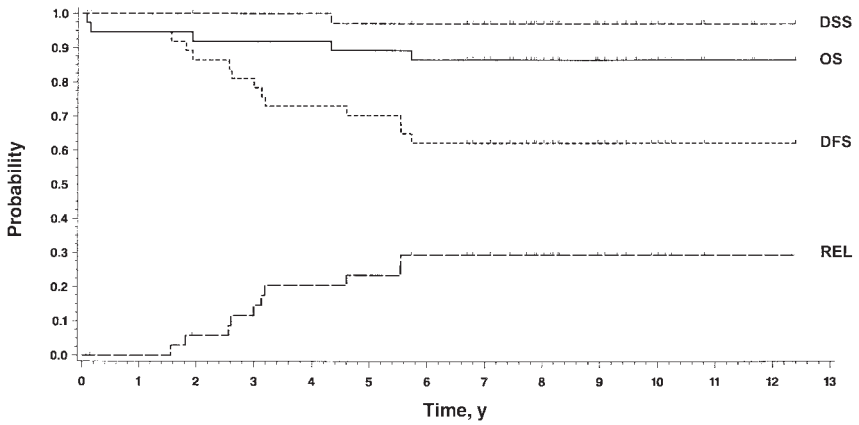

Figure 1. Actuarial disease-specific survival (DSS), overall survival (OS), disease-free survival (DFS), and relapse (REL) following autologous bone marrow transplantation in 37 patients with follicular lymphoma during their first complete (n = 8) or first partial (n = 29) chemotherapy-induced remissions.

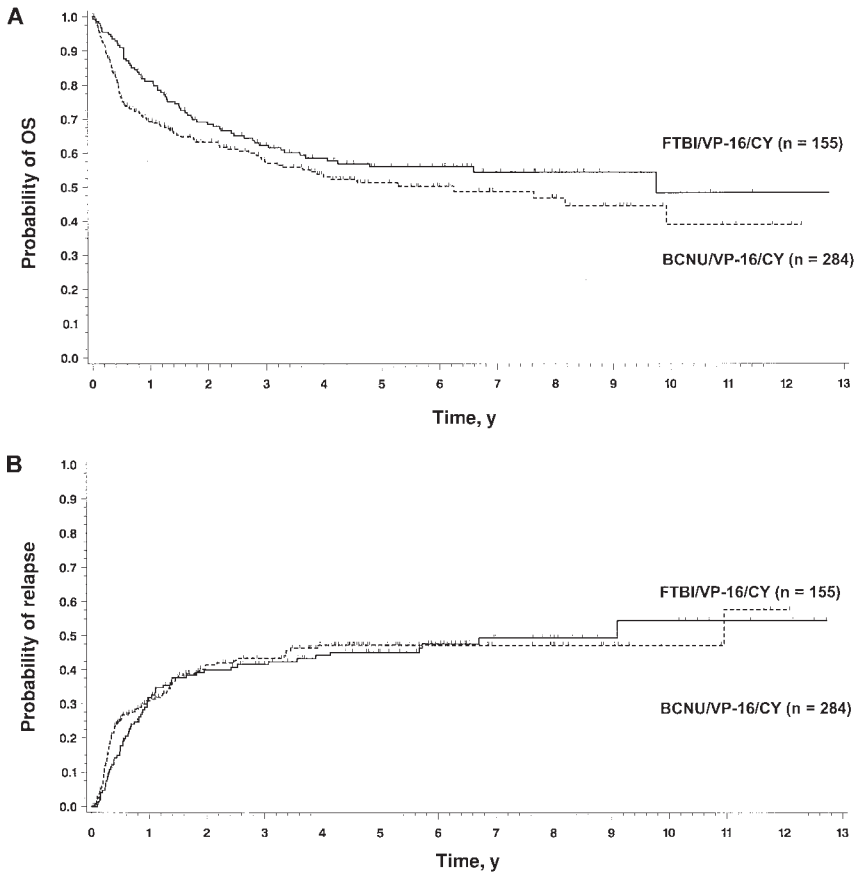

Figure 2. Effect of 2 preparatory regimens (fractionated total body irradiation [FTBI]/etoposide [VP-16]/cyclophosphamide [CY], n = 155 and 1,3-bis[2-chloroethyl]-1-nitrosourea [BCNU]/VP-16/CY, n = 284) on actuarial overall survival (OS) (A) and relapse (B) following autologous hematopoietic cell transplantation in 439 patients with persistent or recurrent non-Hodgkin's lymphoma.

OPTIMIZING THE GRAFT: REMOVAL OF CLONOGENIC TUMOR CELLS WITHOUT LOSS OF ACTIVITY FOR HEMATOPOIETIC RECONSTITUTION

Ten years ago, investigators at the Dana Farber Cancer Institute demonstrated that patients with NHL who received autologous marrow grafts devoid of even the smallest number of detectable tumor cells (as demonstrated by polymerase chain reaction [PCR]) attained statistically superior DFS rates compared with patients whose grafts remained PCR positive for tumor cells after the purging process [9]. During the past decade, bone marrow has been almost completely replaced by peripheral blood as the source for hematopoietic cells. Because of high total nucleated cell quantities in apheresis products, new technical approaches were needed to successfully remove tumor cells without loss of activity for hematopoietic reconstitution. A 2-step method has been developed at our center: in the first step, a large amount of undesired cells (about 80%) is removed by centrifugation over percoll with a yield of approximately 80% $CD34^+$ cells; during the second step, lymphoma cells are removed by MoAb/complement lysis [10]. A survival analysis of 439 patients with either persistent or relapsed NHL is shown in Figure 3. A total of 148 patients received grafts of MoAb-purged marrow cells and 291 patients received MoAb-purged blood cells. There was a trend (P = .07) toward improved OS rates in patients who received blood-cell grafts compared with those who received marrow-cell grafts.

Of note, patients with NHL who do not "mobilize" $CD34^+$ cells adequately into the blood can still successfully undergo AHCT using marrow-derived MoAb-purged grafts [11].

Recent reports indicate that systemic administration of the MoAb directed against the CD20 epitope can lead to successful in vivo purging of CD34-cell–enriched peripheral blood harvests [12,13].

Positive selection of hematopoietic stem cells is another conceptually attractive, albeit technically demanding, approach to attaining tumor-free autologous grafts [14]. This method may play an important future role in AHCT, especially after being simplified and becoming more widely available.

POSTTRANSPLANTATION THERAPY TO CONSOLIDATE REMISSION

Many patients with NHL and other diseases enter a complete remission or MRD state. Such favorable clinical conditions provide an opportunity for consolidation strategies using cytokines, MoAbs, vaccines, specifically engineered cells, local irradiation, posttransplantation chemotherapy, or a combination of several of these modalities.

Cytokines

A combination of interferon and interleukin-2 (IL-2) was administered to 56 NHL patients after AHCT [15]. DFS and

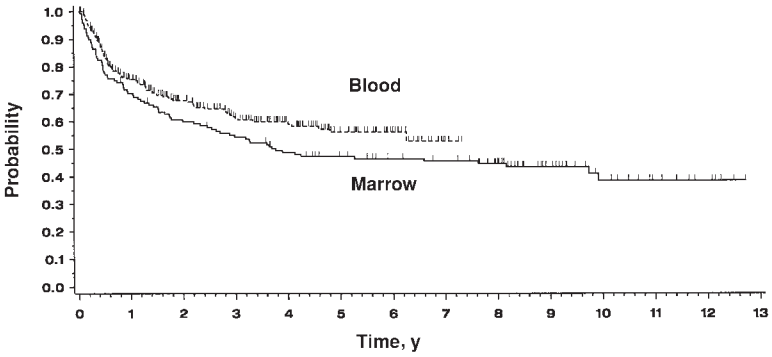

Figure 3. Actuarial overall survival after hematopoietic cell transplantation in 439 patients with persistent or recurrent non-Hodgkin's lymphoma in relation to the source of the monoclonal antibody–purged autologous graft: peripheral blood (n = 291) or bone marrow (n = 148). There was a trend toward improved outcome with blood-derived cells (P = .07).

OS rates of these patients were significantly improved compared with a group of matched historical control patients. A phase III trial to prospectively evaluate this posttransplantation strategy is currently being performed by EBMT. In another trial, the Southwest Oncology Group (SWOG) is testing posttransplantation administration of IL-2 in a randomized fashion, with patients assigned to observation serving as controls (SWOG trial 9438). So far, IL-2 has been reasonably well tolerated with no mortality encountered in relation to the administration of this agent. Accrual to this study should be completed by the end of 2001.

Monoclonal Antibodies

The posttransplantation use of MoAbs has become possible during recent years. Two groups of investigators have explored the chimeric antibody directed against CD20, rituximab [13,16]. A group of investigators at Johns Hopkins University tested the antibody in 25 patients during the graft mobilization phase and again after AHCT, and we administered the MoAb twice to 35 patients with NHL in 4-week courses beginning on day 42 posttransplantation and again on day 180. The data from both trials are sufficiently promising in terms of in vivo purging effect and freedom from relapse following AHCT, so that a phase III trial is being initiated (under the auspices of the Eastern Cooperative Oncology Group, ECOG trial E2499).

Vaccines

Vaccination with the idiotype protein derived from B-cell malignancies can produce idiotype-specific immune responses that correlate with improved remission duration and survival in patients with follicular NHL [17]. A recently completed study at Stanford University indicates that, of 13 AHCT recipients, 11 were able to mount a strong and specific immune response to idiotype vaccines and 8 experienced prolonged remissions lasting from 3 to 11 years (T.A. Davis, F.J. Hsu, C.B. Caspar, et al., unpublished data, 2001). An extended prospective clinical trial is currently being performed at the University of Nebraska (J.M. Vose, MD, written communication, 2001).

Cells

Lymphokine-activated killer cells have been tested with and without IL-2 against a number of hematologic malignancies and solid tumors. In addition to being ineffective in NHL, this treatment was associated with rather extensive toxicities. In contrast, cytokine-induced killer (CIK) cells were well tolerated and led to tumor reductions in a group of patients who had suffered relapses of their diseases after AHCT (R. S. Negrin, MD, unpublished data, 2001). It is now planned to test the effect of CIK cells administered electively after AHCT to patients who are at MRD and who have a high risk of relapse.

Irradiation

Posttransplantation irradiation to areas of prior "bulk" disease is a successful treatment concept for patients with Hodgkin's disease [18,19]. In our experience, a similarly positive effect can be attained in the setting of AHCT for patients with NHL (R. T. Hoppe, MD, unpublished data, 2001).

CONCLUDING REMARKS

The title I have chosen for this presentation is meant as an imperative (hence, the exclamation mark). High-dose combination therapy followed by a so-called "stem cell transplant" is too often an unsuccessful answer to the difficult problems of cancer. It is our responsibility as physicians and clinical investigators to employ all possible methods to achieve an optimal and, it is hoped, a durable response. With "cure" being the ultimate treatment goal for all patients who come to receive AHCT, we need to use all means to improve the outcome of our efforts. Only through continued bench-to-bedside research will new treatment concepts become available. Carefully designed clinical trials are required to prove the therapeutic potential of these novel approaches.

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